REMARKS

Status of the Claims

Pending claims

Claims 1 to 16, 19 to 22 and 24 to 65 are currently pending.

Claims added in the instant amendment

In the present response, claims 66 to 94 are added. Accordingly, after the entry of the instant amendment, claims 1 to 16, 19 to 22 and 24 to 94 will be pending and under examination.

Outstanding Rejections

Claims 1, 27, 57 to 60 and 63 are rejected under the written description requirement of 35 U.S.C. 112, first paragraph. The rejection of claims 31 and 39 under 35 U.S.C. 112, second paragraph, has been maintained (and claims 2 to 10, 27 to 31, 40 to 44, 49 to 51, 54, 55, 61, 62, 64, 65 are rejected under 35 U.S.C. 112, second paragraph, as depending from rejected claims). Claims 1 to 7, 27 to 31, 43, 44, 49 and 57 to 63 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Lauto et al. 2001 (U.S. Patent 6,323,037 B1), filed April 6, 1999 (hereinafter "Lauto"). Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Telephonic interview

Applicants respectfully request a telephonic interview to discuss substantive issues after the Examiner has reviewed the instant response and amendment. Please call Applicants' representative Gregory Einhorn at 858 720 5133.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for claims directed to biomolecular solders, and methods for making and using them, comprising pre-denaturing a proteinaceous substance before placing the

solder *in situ* by partially denaturing the proteinaceous substance while moist with a solvent such that at least a portion of the proteinaceous substance bonds together, can be found, inter alia, on page 11, lines 1 to 6; page 14, lines 16 to 34; page 22, lines 4 to 25; page 28, lines 26 to 28, of the specification (i.e., WO 99/65536). Support for claims directed to biomolecular solders, and methods for making and using them, comprising *in situ* denaturation of the solder (after pre-denaturation), can be found, inter alia, on page 11, lines 26 to 35; page 16, lines 3 to 6; page 23, lines 7 to 21; page 24, lines 1 to 34; page 28, line 29 to page 29, line 10. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the solder comprises any one of an albumin, a collagen, an elastin, a fibrinogen, or any combination thereof can be found, inter alia, on page 7, lines 1 to 17. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the solder comprises human, horse, bovine, rat, ovine or rabbit albumin can be found, inter alia, on page 7, lines 10 to 12 and 29 to 30. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the solder is denatured before or after placing the composition *in situ* comprises use of light, heat, radiation, ultrasound or chemicals, can be found, inter alia, on page 8, lines 24 to 29. Support for claims directed to biomolecular solders, and methods for making and using them, wherein the denatured solder is shaped into a sheet, a tube, a partial tube, a strip, a patch, a hollow tube with a flanged end or a rod before or after placing of the pre-denatured solder *in situ*, can be found, inter alia, on page 9, lines 22 to 25. Support for claims directed to methods for using biomolecular solders wherein a blood vessel, a nerve, a pancreatic duct, a liver vessel or duct, a cystic duct, a tear duct, prostatic duct, a ureter, urethra, an epididymis, a vas, a fallopian tube, a bowel, a bronchi, a gastroenterological tube or duct, a respiratory tube or duct or a brain vessel, tube or duct are welded together, can be found, inter alia, on page 16, lines 19 to 21; page 17, lines 28 to 30; page 18, lines 29 to 36. Support for claims directed to biomolecular solders wherein the composition comprises a proteinaceous substance in a concentration in a range of between about 40% w/w and 80% w/w, or between about 45% w/w and 75% w/w, of the composition, can be found, inter alia, on page 7, lines 23 to 34. Support for claims directed to a sterile biomolecular solder, can be found, inter alia, on page 15, lines 34 to 36.

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Issues under 35 U.S.C. §112, first paragraph

Written Description

Claims 1, 27, 57 to 60 and 63 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention .

Claim 1, as amended, is directed to biomolecular solders made by a method comprising providing a composition comprising a proteinaceous substance in a solvent; and pre-denaturing the proteinaceous substance before placing the composition *in situ* by at least partially denaturing the proteinaceous substance while moist with the solvent such that at least a portion of the proteinaceous substance bonds together.

In particular, it was alleged that a "broad-brush" discussion of making substances that serve as possible proteinaceous solders does not constitute a disclosure of a representative number of members of that class, and no representative number of claimed solders was disclosed that would lend a full description to the entire class that is entailed by claim 1. It was alleged that the specification's general discussion of making proteinaceous solders constitutes an invitation to experiment by trial and error, and, putting the claimed methods into practice awaited someone actually discovering a necessary component of the invention.

In fact, by setting forth several specific examples of proteinaceous substances that can be used in practicing the claimed invention (e.g., in claim 2, where the proteinaceous substance can comprise a protein, such as (e.g., claim 3) albumin, elastin, collagen, fibrinogen, or any combination thereof), Applicants have met the written description requirement. Applicants have satisfied the written description requirement by showing that their invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, including identifying several exemplary species of proteinaceous substances whose structures are well known in the art (e.g., albumin, elastin, collagen, fibrinogen). In its Guidelines, the PTO has determined that the written description

requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106.

Furthermore, the specification described common structural features and common physical properties possessed by all members of the genus of proteinaceous substances used in the claimed methods. The structure of proteinaceous substances, e.g., proteins, such as albumin, elastin, collagen and fibrinogen, were well known in the art. A physical property possessed by all members of the genus is described comprises their ability to bond when denatured, for example, a method comprising denaturing a proteinaceous substance while moist with a solvent such that at least a portion of the proteinaceous substance bonds together. According, the specification set forth a correlation between structure, a physical property possessed by all members of the genus and function.

Because the structure and physical properties (e.g., bonding when denatured) of proteinaceous substances, such as proteins, were well known in the art, disclosure of the use of proteins as proteinaceous substances in the claimed methods alone should be sufficient to meet the written description requirement. However, Applicants have also described several exemplary species (e.g., albumin, elastin, collagen, fibrinogen) of the genus of proteinaceous substances that can be used in the claimed methods, thus providing a specification disclosure that clearly satisfies the written description requirement. In light of disclosure of multiple species of proteinaceous substances that can be used in the claimed methods (e.g., proteins, such as albumin, elastin, collagen, fibrinogen), the Patent Office's remarks that the specification only "constitutes an invitation to experiment" is clearly incorrect.

Furthermore, the specification describes in detail exemplary procedures for practicing the invention. The study described in detail in the specification clearly demonstrates that the claimed methods can be practiced successfully, see, e.g., Example 1, pages 25 to 32 of the

specification (WO 99/65536). Example 1 describes a proof of concept study carried out on 45 subjects (rats) that clearly demonstrates that the methods of the invention can be practiced successfully. It is concluded that "a resorbable protein used as a solder, activated by a diode laser, can provide a reliable, safe and rapid arterial anastomosis, which could be performed by any microsurgeon faster than conventional suturing after a short learning curve" (see page 26, lines 6 to 10). The described exemplary study presents the sutureless, quick and reliable process of the invention that can successfully anastomose small diameter arteries. Because the solders of the invention comprise resorbable protein solders which are at least partially denatured, they can be used to avoid vessel wall fibrosis by eliminating any permanent implanted devices. Accordingly, the Patent Office's remark that the specification only identifies some compounds that might work does not reflect the detailed proof of concept experiments described in the specification.

Issues under 35 U.S.C. §112, second paragraph

Claims 31 and 39 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention (claims 2 to 10, 27 to 31, 40 to 44, 49 to 51, 54, 55, 61, 62, 64, 65 were rejected as depending from rejected claims).

The term "or an analogue thereof" is objected to. The instant amendment addresses this issue.

Issues under 35 U.S.C. §102

Lauto et al. 2001 (U.S. Patent 6,323,037 B1)

Claims 1 to 7, 27 to 31, 43, 44, 49 and 57 to 63 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Lauto.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Applicants respectfully aver that the claimed solders are compositions that are distinctly different from the compositions described by Lauto. The compositions of this invention possess entirely different properties from those described by Lauto. The instant amendment and the discussion below clarify these distinct differences.

The claimed protein-based compositions are distinctly different from those described by Lauto because the solders of the invention are "pre-denatured" prior to use in the body (prior to use *in situ*) – in other words, the solders of the invention are partially or completely denatured *ex vivo*, i.e., during the manufacturing of the solder (however, please note that in one aspect, solders of the invention can be further denatured *in situ*). The "at least partial pre-denaturation" or "precooking" of the proteinaceous material causes a relatively homogenous internal bonding, or crosslinking, of the protein (the cross-linking-denaturation effect can be partial or complete). The result of this "pre-denaturation" cross-linking of proteinaceous material is that the claimed compositions do not substantially dissolve in solution, irrespective of the original water content of the mixture of proteinaceous material and solvent. This substantial insolubility is in contrast to the compositions of Lauto, which remain relatively soluble, as discussed, below.

Furthermore, the invention's "pre-denaturation," cross-linking process produces a solder that is effective *in situ* at a relatively low protein concentration, e.g., at least 50%, 60% or 70% protein mixture. The "pre-denatured," cross-linked solder does not substantially dissolve when immersed in saline. The proteinaceous material has been cross-linked (bound to itself) during the pre-denaturation treatment (which can be partial or complete denaturation). Upon immersion in a hydrating solution, the claimed product hydrates and becomes elastic. There is no loss of proteinaceous material (e.g., albumin) to the solution. If the product is removed from solution and dried the amount of proteinaceous material in the product remains unchanged.

In contrast, Lauto does not "pre-denaturate" (cross-link) its solder *ex vivo*. Lauto does not at least partially denature its solder during its manufacture. Thus, Lauto's solder is structurally distinct from the solder of the instant invention.

Because it is not least partially denatured during its manufacture, Lauto's solder is relatively soluble *in situ*. Lauto needs to use high albumin concentration - above 70% - in its solder to significantly reduce solubility and retain the shape of the final albumin product (see, e.g., column 2, lines 54 to 62; column 6, lines 1 to 10, of Lauto). A high albumin concentration was needed to decrease solubility because Lauto did not pretreat (cross-link) their solder before placing it *in situ*. Lauto's albumin product remains relatively soluble, dissolving at a slow rate (see discussion below). In contrast, this is not the case with the biomolecular solder of this invention. The product of the claimed invention is different (and in some cases superior) because the *ex vivo* cross-linking (at least partial pre-denaturation) step makes the proteinaceous solder insoluble and elastic. It is the instant application that for the first time describes cross-linking of proteinaceous solder *ex vivo* before its placement *in situ*.

In situ solubility differences (e.g., in physiologic solution) denote the structural difference between the solder compositions of the instant claimed invention and the composition described by Lauto. The ability (or inability) of Lauto's albumin compositions to retain their shape at different concentrations in saline is discussed in Example 1, columns 5, line 60 to column 6, line 10:

> After preparation, the samples were placed in 0.5 ml of a saturated saline solution, and the solution was shaken every minute for 2 or 3 seconds. Every few seconds the portion of the composition samples that was not yet dissolved was rescued and observed under a dissecting microscope at fifty times magnification. The 56% composition was completely dissolved after only 3 minutes. The 66% composition was observed to lose its shape and was observed to curl severely and fold after 45 seconds. The 70% composition lost its shape and severely twisted and curled after only 85 seconds. In addition, both the 66% and 70% compositions broke very easily when they were pulled apart with fine forceps, as observed under the microscope. The 75% composition, surprisingly, retained its shape and twisted only slightly after 50 minutes in solution. Furthermore, the 75% composition was appreciably more resistant to being pulled apart with fine forceps than were the lower concentration compositions. (emphasis added)

It is clear Lauto's specification that increased albumin concentration was used to reduce the solubility of their albumin product in saline. However, importantly, the albumin product nevertheless dissolves, but at a slower rate when the albumin concentration is increased.

Alternative aspects of the claimed process can use varying *ex vivo* cross-linking (pre-denaturation) conditions, varying *in situ*-denaturation conditions, or both. The temperature of *ex vivo* cross-linking denaturation can be changed to determine and control the amount of internal strength of the solder. For example, a hydrated albumin product denatured at 90°C has different elasticity to a product denatured at 130°C. However, in all embodiments of the instant invention, the final, *in situ* solder is insoluble, unlike the product described by Lauto.

Thus, the present invention found that *ex vivo*-denaturation ("pre-denaturation") can significantly reduce proteinaceous solder solubility in physiologic solution. Varying denaturation temperature can vary the elasticity and internal strength of the solder product independent of initial protein concentration. In practicing the instant invention, initial protein concentration is only chosen to facilitate the desired shape to be formed, not to impart the insolubility property.

The biomolecular solders of the claimed invention are based on entirely different principles – they are made by entirely different methods (incorporating *ex vivo* cross-linking) - when compared to the compositions of Lauto (which are excited *in situ*). The biomolecular solder of the claimed invention possesses entirely different physico-chemical properties when compared to the compositions of Lauto, as evidenced, e.g., by *in situ* solubility. Thus, the compositions of the claimed invention are a different product. The difference is imparted by *ex vivo* cross-linking (complete or partial "pre-denaturation") of the protein to provide a substantially insoluble proteinaceous solder.

Thus, Applicants submit that because Lauto is not a single prior source that contains each and every limitation of the claimed invention and does not teach or suggest the composition or methods of the instant invention the rejection of the claims under 35 U.S.C. §102(e) may properly be withdrawn.

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CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102(e). The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants submit concurrently herewith a Petition for 2-month Extension of Time and the appropriate Fee Transmittal for the Petition and the additional claim fees. No other fees are believed to be necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket no. 577122000200. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

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Respectfully submitted,

By

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